144 *Bull. Korean Chem. Soc., Vol. 11, No. 2, 1990*

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Conformational Studies of Sulfonylurea Herbicides: Bensulfuron Methyl and Metsulfuron Methyl

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Conformational free energy calculations using an empirical potential function (ECEPP/2) and the hydration shell model were carried out on the sulfonylurea herbicides of bensulfuron methyl (Londax) and metsulfuron methyl (Ally). The conformational energy was minimized from starting conformations which included possible combinations of torsion angles in the molecule. The conformational entropy of each conformation was computed using a harmonic approximation. To understand the hydration effect on the conformtion of the molecule in aqueous solution, the hydration free energy of each group was calculated and compared each other. It was found that the low-free-energy conformaitons of two molecules in aqueous solution prefer the overall folded structure, in which an interaction between the carbonyl group of ester in aryl ring and the first amido group of urea bridge plays an important role. From the analysis of total free energy, the hydration and conformational entropy are known to be essential in stabilizing low-free-energy conformations of Londax, whereas the conformational energy is proved to be a major contribution to the total free energy of low-free-energy conformations of Ally.

Introduction

Sulfonylureas are one of new classes of high potency herbicides which show excellent weed control activity at extremely low application rates (4-35 grams per hectare).[1,2] It has been known that the herbicidal potency of the sulfonylureas is due to their ability to inhibit the enzyme, acetolactate synthase (ALS).[3] This enzyme catalyzes the first common step in the biosynthesis of the essential branched chain amino acids, valine and isoleucine. Studies on enzyme kinetics show that sulfonylurea acts as slow tight-binding inhibitors.[4-6] Although the inhibition of the enzyme by sulfonylurea herbicides has been recently studied using enzyme kinetics and biotechnologies, the detailed conformations of sulfonylurea herbicides alone and the ALS enzyme are not well reported. In this work, the conformation of sulfonylurea herbicides such as bensulfuron methyl (Londax) and metsulfuron methyl (Ally) in aqueous solution was studied as a first step in understanding an interaction of sulfonylurea herbicides with the ALS enzyme.

The sulfonylurea herbicide is composed of an aryl group, sulfonylurea bridge, and a nitrogen-containing heterocycle. Londax and Ally have differences in chemical structure of sulfonylurea bridge and heterocycle (see Figure 1). Londax has a modified bridge (*i.e.*, -CH$_2$SO$_2$NHCONH-) and a pyrimidine ring containing two methoxy substituents, whereas Ally has an unmodified bridge and a triazine containing methyl and methoxy substituents at the same positions as in a pyrimidine ring of Londax.

Methods

The nomenclature and conventions used for torsion angles follow the recommendations of the IUPAC Commission on Nomenclature of Organic Chemistry.[7] The bond lengths and bond angles adopted for the molecules were taken as
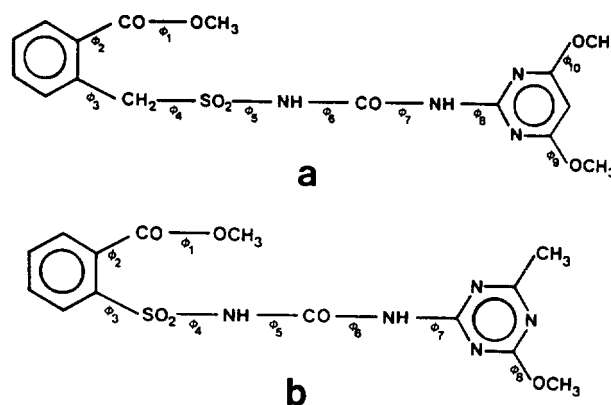

Figure 1. Definition of torsion angle variables of (a) Londax and (b) Ally.

similar values in a general literature.[8] In conformational energy calculations, bond lengths and bond angles were fixed and only the torsion angles for internal rotation were taken as the variables. The definition of torsion angles in the molecules is shown in Figure 1.

The conformational energy computations were carried out with ECEPP/2,[9] whose potential parameters were originally optimized to give a good fit of calculated physical and thermodynamic quantities of organic molecules with various functional groups to experimental values. The total conformational energy is the sum of the electrostatic, the non-bonded, and the torsional energies. The hydrogen-bond energy is included in the nonbonded energy component. The partial charge for each atom of the molecule was determined using the CNDO/2 (ON) method[10] for the fully extended conformation. The hydration shell model improved recently[11] was used to compute the hydration free energy of each conformation of the molecules in the hydrated state, where the hydration free energy was obtained as the sum of two contributions from water-accessible volume and polarization (see ref. 11 for details). To minimize the conformational energy, a variable metric algorithm SUMSL[12] was used. All the torsion

Table 1. Energetics of Low-Free-Energy Conformations of Londax[a,b]

Conformation[c]	$\Delta G_{tot}{}^{d}$	ω^{e}	ΔE^{f}	ΔG^{g}	$-T\Delta S^{h}$	$\Delta\Delta G_{hyd}{}^{i}$	$\Delta E_{es}{}^{j}$	$\Delta E_{nb}{}^{k}$	$\Delta E_{tor}{}^{l}$
$g^-g^-tg^+$	0.00	0.279	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$g^+g^+tg^-$	0.06	0.251	0.00	0.06	0.06	0.00	0.01	0.00	-0.02
$g^-g^-tg^-$	0.28	0.174	-0.42	-0.05	0.37	0.33	-0.29	-0.03	-0.10
$g^+g^-tg^+$	0.28	0.173	-0.42	-0.05	0.38	0.33	-0.29	-0.03	-0.10
$g^-g^-g^+t$	1.67	0.017	-0.96	-0.11	0.85	1.78	0.27	-1.51	0.29
$g^+g^-g^+t$	1.85	0.012	-2.28	-0.82	1.46	2.67	0.29	-2.35	-0.22
g^-g^+tt	2.15	0.007	1.30	1.25	-0.05	0.91	-1.53	-0.08	-0.16
g^+g^-tt	2.15	0.007	1.30	1.25	-0.05	0.91	1.53	-0.07	-0.16
$g^-g^-tg^+$	2.22	0.007	-1.02	0.44	1.45	1.78	0.18	-0.88	-0.32
$g^-g^-tg^-$	2.22	0.007	0.22	1.06	0.84	1.16	-0.35	-0.91	1.48
$g^+g^-tg^-$	2.23	0.006	-1.02	0.44	1.46	1.78	0.18	-0.88	-0.32
$g^+g^-tg^+$	2.25	0.006	0.22	1.09	0.86	1.16	-0.35	-0.91	1.48
g^-g^-tt	2.27	0.006	1.96	1.67	-0.28	0.59	2.09	0.04	-0.17
g^+g^+tt	2.28	0.006	1.96	1.68	-0.27	0.59	2.09	0.04	-0.17
g^+g^+tt	2.28	0.006	1.96	1.68	-0.29	0.61	2.08	0.07	-0.18
$g^-g^-tg^+$	2.50	0.004	0.82	1.54	0.72	0.96	0.22	-0.91	1.50
$g^+g^+tg^-$	2.52	0.004	0.82	1.55	0.73	0.97	0.23	-0.90	1.50
$g^-g^-tg^-$	2.61	0.003	-0.41	1.20	1.62	1.41	0.67	-0.96	-0.12
$g^+g^+tg^+$	2.61	0.003	-0.41	1.20	1.62	1.41	0.67	-0.95	-0.13
$g^+g^+tg^+$	2.85	0.002	-0.49	0.89	1.37	1.97	0.85	-1.34	0.00
$g^-g^-tg^-$	2.86	0.002	-0.49	0.89	1.38	1.97	0.86	-1.35	0.00
$g^+g^+g^-g^-$	2.90	0.002	-2.17	-0.43	1.75	3.33	-0.77	-1.36	-0.04
$g^-g^-g^+g^+$	2.92	0.002	-2.17	-0.42	1.76	3.34	-0.77	-1.34	-0.07
$g^-g^+g^-g^+$	2.92	0.002	-3.28	-2.28	1.00	5.20	0.00	-1.80	-1.48
$g^+g^-g^+g^-$	2.94	0.002	-3.28	-2.29	0.99	5.23	0.00	-1.81	-1.47

[a]Energies are in kcal/mol and free energies and entropic contributions are calculated at 298 K. [b]Only the conformations with the total free energy change $\Delta G_{tot} < 3$ kcal/mol are listed. [c]Each conformation is defined by four torsion angles of ϕ_2, ϕ_3, ϕ_4, and ϕ_5 defined in Figure 1a: $0°\leq g^+ \leq 120°$, $-120°\leq g^- \leq 0°$, $120°\leq t \leq 180°$ or $-180°\leq t \leq -120°$. [d]The total free energy of each conformation in the hydrated state; $G_{tot} = G - G_{tot}{}^{o}$, $G_{tot}{}^{o} = -45.29$ kcal/mol. [e]Normalized statistical weight. [f]Intramolecular interaction energy change: $\Delta E = E - E^{o}$, $E^{o} = -111.48$ kcal/mol. [g]Free energy change: $\Delta G = \Delta E - T\Delta S$, $G^{o} = 2.83$ kcal/mol. [h]Conformational entropic contribution. [i]Hydration free energy of each conformation; $\Delta\Delta G_{hyd} = \Delta G_{hyd} - \Delta G_{hyd}{}^{o}$, $\Delta G_{hyd}{}^{o} = -48.12$ kcal/mol. [j]Electrostatic energy change; $\Delta E_{es} = E_{es} - E_{es}{}^{o}$, $E_{es}{}^{o} = -107.56$ kcal/mol. [k]Nonbonded energy change; $\Delta E_{nb} = E_{nb} - E_{nb}{}^{o}$, $E_{nb}{}^{o} = -6.15$ kcal/mol. [l]Torsional energy change; $\Delta E_{tor} = E_{tor} - E_{tor}{}^{o}$, $E_{tor}{}^{o} = 2.23$ kcal/mol.

angles of the molecules were allowed to vary during minimization.

For Londax, the 81 conformations were selected as starting points for energy minimization from the four combinations of ±60° and 180° for ϕ_2, ϕ_3, ϕ_4, and ϕ_5. To torsion angles ϕ_1, ϕ_6, ϕ_7, and ϕ_8, 180° was assigned with ϕ_9 and ϕ_{10} equal to 0°. The selection of these angles were based on the similar structures in literature,[8] especially for ϕ_9 and ϕ_{10} from ref. 13. These 10 torsion angles were allowed to vary during energy minimization of Londax.

The 54 conformations were used as starting points for energy minimization of Ally from the four combinations of ±60° and 180° for ϕ_2, ϕ_3, and ϕ_4, and of 0° and 180° for ϕ_7. The remaining torsion angles ϕ_1, ϕ_5, and ϕ_6 were assigned to be 180°, except ϕ_8 equal to 0°. These 8 torsion angles were also allowed to move during minimization of Ally.

For each conformation obtained by minimization of the unhydrated molecules, the hydration free energy was computed without further minimization, because minimization of the total energy of hydrated molecules takes much computation time and the hydration does not largely alter the confor-

mations.[14]

At each energy minimum in the unhydrated state, the conformational entropy was computed using a harmonic method of Go et al.[15] The elements of a hessian matrix of second derivatives at each minimum were numerically calculated.[16] The seven- and five-point formulas were employed for the calculation of off-diagonal and diagonal elements, respectively, with the step size of each variable equal to 1°.

The relative total free energy is given by $\Delta G_{tot} = \Delta G + \Delta\Delta G_{hyd}$, where ΔG is the relative conformational free energy (i.e., $\Delta G = G - G^{o}$, where G^{o} is the free energy of the conformation of the lowest free energy), and $\Delta\Delta G_{hyd}$ is the relative hydration free energy (i.e., $\Delta\Delta G_{hyd} = \Delta G_{hyd} - \Delta G_{hyd}{}^{o}$, where $\Delta G_{hyd}{}^{o}$ is the hydration free energy of the conformation of lowest free energy). The relative conformational energy is given by $\Delta E = E - E^{o}$, where E^{o} is the conformational energy of the conformation of lowest free energy. The relative entropic contribution to the relative free energy is given by $-T\Delta S$. Also the normalized statistical weight of each conformation was computed using an equation of Zimmerman et al.[17] All the thermodynamic quantities have been calculated for $T = 25\,°C$.

146 *Bull. Korean Chem. Soc., Vol. 11, No. 2, 1990*

Young Kee Kang and Dae Whang Kim

Table 2. Torsion Angles of Low–Free–Energy Conformations of Londax[a,b]

Conformation[c]	ϕ_1	ϕ_2	ϕ_3	ϕ_4	ϕ_5	ϕ_6	ϕ_7	ϕ_8	ϕ_9	ϕ_{10}
$g^-g^-tg^+$	179	-88	-98	168	62	179	167	166	2	0
$g^+g^+tg^-$	-179	87	98	-168	-62	-179	-167	-166	-2	0
$g^-g^+tg^-$	176	-96	96	-173	-64	-179	-167	-166	-2	0
$g^+g^-tg^+$	-176	97	-96	173	64	179	167	166	2	0
$g^-g^-g^+t$	179	-93	-101	53	-150	178	-165	-165	0	1
$g^+g^-g^+t$	178	78	-101	62	-170	179	167	166	2	1
g^-g^+tt	175	-98	95	-175	179	-180	167	166	2	0
g^+g^-tt	-175	98	-95	174	-179	180	-167	-166	-2	0
$g^-g^+tg^+$	174	-98	95	180	66	179	-168	-167	-6	0
$g^-g^+tg^-$	178	-101	79	126	-64	-179	168	167	1	0
$g^+g^-tg^-$	-174	98	-95	-180	-65	-179	168	167	6	0
$g^+g^-tg^+$	-178	101	-79	-126	64	179	-168	-167	-1	0
g^-g^-tt	180	-85	-98	173	179	180	-167	-166	-2	0
g^+g^+tt	-180	84	98	-173	-179	-180	167	166	1	0
g^+g^+tt	-180	85	98	-173	-178	-180	-167	-166	-2	1
$g^-g^-tg^+$	176	-76	-78	-128	63	178	-168	-167	-1	0
$g^+g^+tg^-$	-176	76	78	128	-63	-178	168	167	1	0
$g^-g^-tg^-$	176	-78	-94	-176	-64	-179	-167	-167	-6	1
$g^+g^+tg^+$	-176	78	94	176	64	179	167	167	6	-1
$g^+g^+tg^+$	-178	84	98	-168	67	179	-167	-166	0	0
$g^-g^-tg^-$	178	-84	-98	168	-67	-179	167	166	0	0
$g^+g^+g^-g^-$	-179	77	98	-79	-69	-179	169	166	1	0
$g^-g^-g^+g^+$	179	-77	-98	79	69	179	-169	-166	-1	1
$g^-g^+g^-g^+$	178	-96	98	-54	86	-179	173	173	10	0
$g^+g^-g^+g^-$	-178	96	-98	54	-86	179	-173	-173	-10	0

[a]Units are in degree. [b]See Figure 1a for definition of torsion angles. [c]See footnotes of Table 1 for denotation of each conformation.

Results and Discussion

Energetics of low–free–energy conformations (*i.e.*, $\Delta G_{tot} < 3$ kcal/mol) in the hydrated state, their torsion angles, and hydration free energy of each group are listed in Tables 1–3 for Londax and in Tables 4–6 for Ally. For each conformation, Tables 1 and 4 contain (1) the conformational letter codes, (2) the relative total free energy ΔG_{tot}, (3) the normalized statistical weight ω, (4) the relative conformational energy ΔE, (5) the relative conformational free energy ΔG, (6) the relative entropic contribution to conformational free energy $-T\Delta S$, (7) the relative hydration free energy $\Delta\Delta G_{hyd}$, and (8) the relative energy components ΔE_{es}, ΔE_{nb}, and ΔE_{tor} of ΔE. For each conformation, a four-letter conformational code is used for torsion angles ϕ_2, ϕ_3, ϕ_4, and ϕ_5 of Londax, and for torsion angles ϕ_2, ϕ_3, ϕ_4, and ϕ_7 of Ally.

Bensulfuron Methyl (Londax). From the 81 starting conformations of Londax, the only 25 conformations have the relative total free energy (ΔG_{tot}) less than 3 kcal/mol. Four conformations with $\Delta G_{tot} < 1$ kcal/mol seem to be most probable conformations of Londax in aqueous solution, and these low–free–energy conformations are drawn in Figure 2. There is a common characteristic in torsion angles of these four conformations, *i.e.*, torsion angles ϕ_2, ϕ_3, and ϕ_5 are in *gauche* and torsion angle ϕ_4 in *tans* (see Table 2). The carbonyl group of ester in *ortho* position of phenyl ring is located close to the first amido group of urea bridge though without a strong intramolecular hydrogen bond. If the isolated confor-

mation of Londax is conserved while interacting with the ALS enzyme, the computed low–free–energy conformation tells us that the amido group is essential for the interaction with *ortho* substituents (e.g. ester or halogen group) to the bridge and that sulfonyl oxygens and carbonyl oxygen of sulfonylurea are enabled to interact with the receptor site of the ALS enzyme. Overall a folded conformation is formed between phenyl ring and sulfonylurea bridge, whereas the heterocycle being extended to the bridge. As a result, phenyl and pyrimidine rings keep to some extent far away each other. During the energy minimization, torsion angles ϕ_2, ϕ_3, ϕ_4, ϕ_7, and ϕ_8 moved somewhat largely, while the other torsion angles were varied within $\pm 4°$ from initial values.

The calculated thermodynamic quantities for the low–free–energy conformations of Londax are shown in Table 1. From the analysis of total free energies of the first four low–free–energy conformations, the hydration and conformational entropy are the major contribution to the total free energy. Comparing only the conformational energies, conformations $g^-g^+tg^-$ and $g^+g^-tg^+$ are more stable than conformations $g^-g^-tg^+$ and $g^+g^+tg^-$, and the electrostatic energy (ΔE_{es}) significantly contributes to the total conformational energy. Although conformation $g^+g^-g^+t$ has the lowest conformational energy (*i.e.*, $\Delta E = -2.28$ kcal/mol relative to that of conformation $g^-g^-tg^+$), the total free energy shows somewhat a high value, 1.85 kcal/mol, which comes from contributions of the conformational entropy and hydration (*i.e.*, $-T\Delta S = 1.46$ kcal/mol and $\Delta\Delta G_{hyd} = 2.67$ kcal/mol). Conformations $g^-g^-g^+t$, $g^-g^+tg^+$, and $g^+g^-tg^-$

Table 3. Hydration Free Energy of Each Group of Low–Free–Energy Conformations of Londax[a,b]

Conformation[c]	CO_2Me	Aryl CH_2	SO_2	NHCONH	Pyrimidinyl[d]
$g^-g^-tg^+$	0.00	0.00	0.00	0.00	0.00
$g^+g^+tg^-$	0.00	0.00	0.00	0.00	0.00
$g^-g^+tg^-$	0.02	0.00	0.29	0.02	0.00
$g^+g^-tg^+$	0.02	0.00	0.29	0.02	0.00
$g^-g^-g^+t$	-0.17	0.10	0.00	1.85	0.00
$g^+g^-g^+t$	0.02	0.06	0.17	2.39	0.03
g^-g^+tt	0.00	-0.02	0.80	0.19	-0.08
g^+g^-tt	0.00	-0.02	0.80	0.19	-0.08
$g^-g^+tg^+$	0.52	0.01	0.32	0.67	0.27
$g^-g^+tg^-$	0.09	0.06	0.62	0.31	0.09
$g^+g^-tg^-$	0.52	0.01	0.32	0.67	0.27
$g^+g^-tg^+$	0.09	0.06	0.62	0.31	0.09
g^-g^-tt	0.01	-0.01	0.57	0.10	-0.08
g^+g^+tt	0.01	-0.01	0.57	0.10	-0.08
g^+g^+tt	0.01	0.00	0.58	0.10	-0.08
$g^-g^-tg^+$	0.09	0.06	0.47	0.27	0.08
$g^+g^+tg^-$	0.09	0.06	0.47	0.27	0.08
$g^-g^-tg^-$	0.52	0.01	0.11	0.49	0.27
$g^+g^+tg^+$	0.52	0.01	0.11	0.50	0.27
$g^+g^+tg^+$	0.65	0.02	0.06	0.83	0.40
$g^-g^-tg^-$	0.65	0.02	0.06	0.83	0.40
$g^+g^+g^-g^-$	0.48	0.08	-0.37	2.23	0.92
$g^-g^-g^+g^+$	0.48	0.08	-0.37	2.23	0.92
$g^-g^+g^-g^+$	0.32	0.31	-0.15	3.42	1.30
$g^+g^-g^+g^-$	0.32	0.31	-0.15	3.42	1.33

[a] Energies are in kcal/mol. [b] Relative energies to conformation $g^-g^-tg^+$. [c] Conformational letter codes. [d] $(OMe)_2$pyrimidinyl.

Table 5. Torsion Angles of Low–Free–Energy Conformations of Ally[a,b]

Conformation[c]	ϕ_1	ϕ_2	ϕ_3	ϕ_4	ϕ_5	ϕ_6	ϕ_7	ϕ_8
$g^-g^-g^-g^+$	174	-90	-59	-46	179	-159	26	0
$g^+g^+g^+g^-$	-174	90	59	46	-179	159	-25	0
$g^-g^-g^-t$	174	-85	-57	-43	177	-156	-157	0
$g^+g^+g^+t$	-174	85	57	43	-177	156	157	0
g^-tg^-t	174	-105	161	-60	-179	-158	-156	0
g^+tg^+t	-174	105	-161	60	179	158	156	0
$g^+tg^+g^-$	-174	105	-162	62	178	160	-26	1
$g^-tg^-g^+$	173	-105	162	-62	-178	-160	26	-1
g^-tg^+t	173	-69	-161	60	179	158	156	0
g^+tg^-t	-173	69	161	-60	-179	-158	-156	0
$g^+tg^-g^+$	-173	69	162	-62	-178	-160	26	-1
$g^-tg^+g^-$	173	-69	-162	62	178	160	-26	1
$g^+g^-g^-g^+$	-178	101	-53	-46	178	-158	25	0
$g^-g^+g^+g^-$	178	-101	53	46	-178	158	-25	0
$g^+tg^-g^-$	-173	69	162	-64	-178	162	-27	1
$g^-g^-tg^+$	172	-98	-60	-172	-180	-162	27	-1
g^+g^+tt	-172	99	60	172	-180	162	154	0
$g^+g^-g^-t$	-177	103	-52	-43	177	-156	-157	0
$g^-g^+g^+t$	177	-103	52	43	-177	156	157	0

[a] Units are in degree. [b] See Figure 1b for definition of torsion angles. [c] See footnotes of Table 4 for denotation of conformation.

yield the similar trend. All extended conformation *tttt* has a high free energy larger than 3 kcal/mol, though this conformation was included in starting conformations.

To elucidate the hydration effect on the conformation in detail, the hydration free energy of each group of Londax

Table 4. Energetics of Low–Free–Energy Conformations of Ally[a,b]

Conformation[c]	ΔG_{tot}^d	ω^e	ΔE^f	ΔG^g	$-T\Delta S^h$	$\Delta\Delta G_{hyd}^j$	ΔE_{el}^j	ΔE_{nb}^k	ΔE_{tor}^l
$g^-g^-g^-g^+$	0.00	0.227	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$g^+g^+g^+g^-$	0.01	0.225	0.00	0.00	0.00	0.01	0.01	0.03	-0.03
$g^-g^-g^-t$	0.38	0.118	-1.36	-1.09	0.27	1.48	-0.01	-1.58	0.22
$g^+g^+g^+t$	0.39	0.117	-1.36	-1.09	0.27	1.48	-0.01	-1.57	0.21
g^-tg^-t	1.00	0.042	1.70	2.19	0.49	-1.19	1.08	0.22	0.40
g^+tg^+t	1.01	0.042	1.70	2.19	0.50	-1.19	1.08	0.22	0.40
$g^+tg^+g^-$	1.04	0.039	2.80	3.17	0.36	-2.12	1.21	1.18	0.41
$g^-tg^-g^+$	1.05	0.038	2.80	3.17	0.37	-2.12	1.21	1.19	0.40
g^-tg^+t	1.32	0.025	1.70	2.28	0.58	-0.97	1.07	0.21	0.42
g^+tg^-t	1.32	0.024	1.70	2.29	0.59	-0.97	1.07	0.21	0.43
$g^+tg^-g^+$	1.36	0.023	2.81	3.26	0.45	-1.91	1.21	1.18	0.43
$g^-tg^+g^-$	1.36	0.023	2.81	3.27	0.46	-1.91	1.20	1.18	0.43
$g^+g^-g^-g^+$	1.76	0.012	0.15	0.55	0.39	1.21	0.64	-0.61	0.12
$g^-g^+g^+g^-$	1.79	0.011	0.15	0.56	0.41	1.23	0.65	-0.59	0.09
$g^+tg^-g^-$	1.80	0.011	3.31	3.73	0.42	-1.93	1.43	1.61	0.27
$g^-g^-tg^+$	2.11	0.006	3.10	2.75	-0.34	-0.65	2.11	1.08	-0.09
g^+g^+tt	2.11	0.006	2.19	1.92	-0.27	0.20	1.85	0.65	-0.31
$g^+g^-g^-t$	2.29	0.005	-1.27	-0.57	0.71	2.85	0.56	-2.16	0.33
$g^-g^+g^+t$	2.30	0.005	-1.27	-0.56	0.71	2.87	0.56	-2.17	0.33

[a,b,d,i-l] See footnotes of Table 1. [c] Each conformation is defined by four torsion angles of ϕ_2, ϕ_3, ϕ_4, and ϕ_7 defined in Figure 1b; see footnote c of Table 1 for definition of g^+, g^-, and t. [d] $G_{tot}^o = -53.70$ kcal/mol. [f] $E^o = -127.00$ kcal/mol. [g] $\Delta G^o = 1.80$ kcal/mol. [i] $\Delta G_{hyd}^o = -55.49$ kcal/mol. [j] $E_{el}^o = -126.17$ kcal/mol. [k] $E_{nb}^o = -6.75$ kcal/mol. [l] $E_{tor}^o = 5.92$ kcal/mol.

148 *Bull. Korean Chem. Soc., Vol. 11, No. 2, 1990*

Young Kee Kang and Dae Whang Kim

Table 6. Hydration Free Energy of Each Group of Low-Free-Energy Conformations of Ally[a,b]

Conformation[c]	CO$_2$Me	Aryl	SO$_2$	NHCONH	Triazinyl[d]
$g^-g^-g^-g^+$	0.00	0.00	0.00	0.00	0.00
$g^+g^+g^+g^-$	0.00	0.00	0.00	0.00	0.00
$g^-g^-g^-t$	0.26	0.08	0.13	0.44	0.56
$g^+g^+g^+t$	0.26	0.08	0.13	0.44	0.56
g^-tg^-t	-1.00	-0.01	0.61	-0.86	0.08
g^+tg^+t	-1.01	-0.01	0.61	-0.86	0.08
$g^+tg^+g^-$	-1.01	-0.07	0.53	-1.23	-0.34
$g^-tg^-g^+$	-1.01	-0.07	0.53	-1.23	-0.34
g^-tg^+t	-1.00	-0.01	0.84	-0.88	0.08
g^+tg^-t	-1.00	-0.01	0.84	-0.88	0.08
$g^+tg^-g^+$	-1.01	-0.07	0.76	-1.26	-0.34
$g^-tg^+g^-$	-1.01	-0.07	0.76	-1.26	-0.34
$g^+g^-g^-g^+$	0.34	0.02	-0.11	0.62	0.35
$g^-g^+g^+g^-$	0.34	0.02	-0.11	0.63	0.35
$g^+tg^-g^-$	-1.01	-0.11	0.85	-1.21	-0.45
$g^-g^-tg^+$	-0.53	-0.16	0.75	-0.10	-0.61
g^+g^+tt	-0.54	-0.16	0.91	0.28	-0.30
$g^+g^-g^-t$	0.66	0.10	-0.01	1.04	1.08
$g^-g^+g^+t$	0.66	0.10	-0.01	1.04	1.08

[a] Energies are in kcal/mol. [b] Relative energies to conformation $g^-g^-g^-g^+$. [c] Conformational letter codes. [d] MeOMe triazinyl.

relative to conformation $g^-g^-tg^+$ is shown in Table 3. In general, the contribution of SO$_2$ and NHCONH groups to hydration free energies is significant for lower-free-energy conformations, whereas all the groups except aryl CH$_2$ group contribute to hydration free energies of higher-free-energy conformations. Although conformations $g^-g^-g^-t$ and $g^+g^+g^+t$ have lower conformational energies rather than conformations $g^-g^-g^-g^+$ and $g^+g^+g^+g^-$, the latter conformations are more probable in aqueous solution through the hydration of SO$_2$ group (see Table 3).

Metsulfuron Methyl (Ally). The 19 conformations are found to have the relative total free energy (ΔG_{tot}) less than 3 kcal/mol from the 54 starting conformations. Four conformations with $\Delta G_{tot} < 1$ kcal/mol seem to be most feasible conformations of Ally in aqueous solution, and are shown in Figure 3. Torsion angles of these four conformations have a common characteristic, i.e., torsion angles ϕ_2, ϕ_3, and ϕ_4 are in *gauche* and torsion angle ϕ_7 in *gauche* or *trans* shown in Table 5. Especially, torsion angle ϕ_3 shows *gauche* conformation, whereas the corresponding torsion angle ϕ_4 of Londax is *trans*. Also torsion angle ϕ_7 is *gauche* or *trans*, but the corresponding torsion angle ϕ_8 of Londax shows *trans* conformation only. The overall conformations of low-free-energy states are similar to those of Londax, i.e., the folded conformations are more favorable though there is no strong intramolecular hydrogen bond. However, the orientation of aryl and heterocyclic rings of Ally is different from that of Londax. Phenyl and triazine rings of Ally keep closer and stack to some extent each other (see Figures 2 and 3). So the CH$_2$ group located between aryl ring and sulfonylurea bridge is believed to be an important factor in determining the orientation of two rings. During the energy minimization, there is a large movement in torsion angles ϕ_2, ϕ_3, ϕ_6, and ϕ_7 of
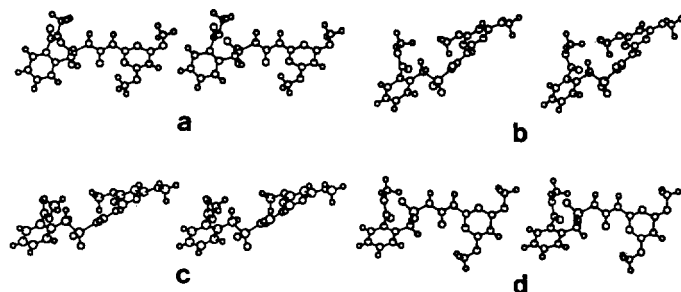

Figure 2. Stereoview of low-free-energy conformations of Londax with $\Delta G_{tot} < 1$ kcal/mol: (a) $g^-g^-tg^+$, (b) $g^+g^+tg^-$, (c) $g^-g^+tg^-$, and (d) $g^+g^-tg^+$.
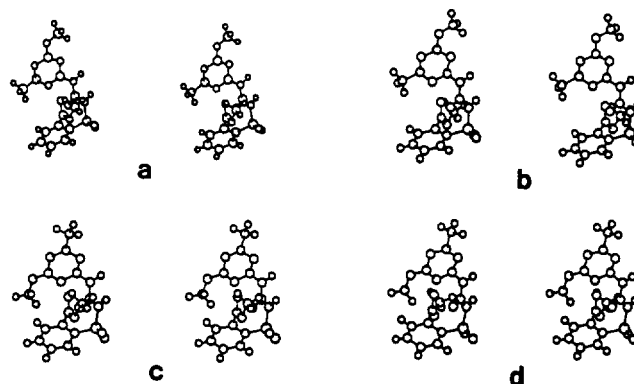
Figure 3. Stereoview of low-free-energy conformations of Ally with $\Delta G_{tot} < 1$ kcal/mol: (a) $g^-g^-g^-g^+$, (b) $g^+g^+g^+g^-$, (c) $g^-g^-g^-t$, and (d) $g^+g^+g^+t$.

all the conformations and in torsion angle ϕ_4 of lower-free-energy conformations, while the other torsion angles show small variations within ±6° from initial values.

Table 4 shows the calculated thermodynamic quantities for low-free-energy conformations of Ally. From analyzing the total free energies of the first four low-free-energy conformations, the conformational energy and hydration contribute largely to the total free energy. Some conformations such as $g^+tg^+g^-$, $g^-tg^-g^+$, $g^+tg^-g^+$, $g^-tg^+g^-$, and $g^+tg^-g^-$ favor the hydration more than the lowest-free-energy conformations $g^-g^-g^-g^+$, $g^+g^+g^+g^-$, $g^-g^-g^-t$, and $g^+g^+g^+t$, but the higher conformational energies coming from the destabilizing electrostatic (ΔE_{es}) and nonbonded (ΔE_{nb}) energies make the former conformations less feasible in aqueous solution. This may be caused from that the interaction between the carbonyl group of ester in aryl ring and the first amido group of urea bridge of the latter conformations is stronger than that of the former conformations (i.e., the average distance between the carbonyl oxygen and the amino hydrogen, R(CO...NH), is 3.1 Å for the latter conformations and is greater than 3.5 Å for the former conformations). Also the shorter average distance of R(CO...NH) of Allyl than that of Londax is coming through missing the CH$_2$ group between aryl ring and sulfonylurea group, where R(CO...NH) of Londax is greater than 3.5 Å. The results show that the conformational entropies do not contribute seriously to the total free energy energies. As done for Londax, all extended conformation *tttt* was included in starting conformations, but shows a high free-energy larger than 3 kcal/mol.

Hydration free energy of each group of Ally relative to conformation $g^-g^-g^-g^+$ is listed in Table 6 to see the detailed hydration effect on each conformation. In general, the hydration of SO_2 and triazinyl groups is favorable in lower-free-energy conformations, and relatively higher-free-energy conformations prefer the hydration of CO_2Me, aryl, and NHCONH groups, differently from the hydration of Londax.

The approach used in this work may have the advantage to calculate the free energy for biomolecules and drugs of interest in aqueous solution over other methods used in conformational studies, especially based on computer simulations. The conformations of sulfonylurea herbicides of Londax and Ally in aqueous solution were studied in terms of conformational energy, conformational entropy, and hydration free energy. The contributions of these terms to the total free energy of each conformation were analyzed and compared each other. From the calculations, it is known that the hydration and conformational entropy are the major contributions to stabilize the low-free-energy conformations of Landax, whereas the conformational energy and hydration contribute largely to the total free energies of low-free-energy conformations of Ally. Also the CH_2 group between aryl and sulfonylurea groups is proved to be essential for conformations and thermodynamics of sulfonylurea herbicides. Sufficient and detailed spectroscopic data of these herbicides will serve as a good check on the present approach. If the conformation of the ALS enzyme is known, the biochemical and physiological function of sulfonylurea in inhibiting the ALS enzyme would be understood from the conformational study on their complex in aqueous solution.

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